Synthesis of Novel, Chiral Bicyclo[3.1.0]hex-2-ene Amino Acid Derivatives as Useful Synthons in Medicinal Chemistry

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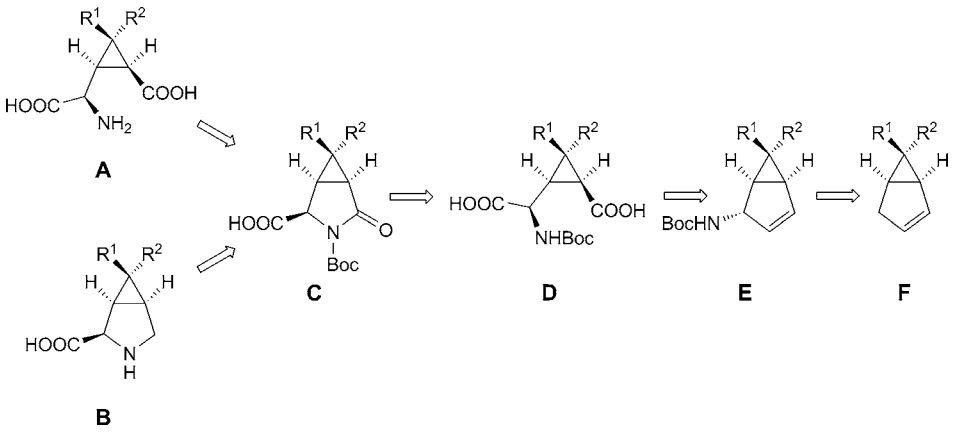
A short and concise synthesis of novel, chiral bicyclo[3.1.0]hex-2-ene amino acid derivatives **13** and **14** has been developed. The key step is a stereo- and regioselective allylic amination of *exo*- and *endo*-methyl bicyclo[3.1.0]hex-2-ene-6-carboxylates **8** and **9**, which were prepared from 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (**1**). These amino acid derivatives are useful building blocks in medicinal chemistry and can be prepared as chiral compounds by using either (+)-**1** or (−)-**1** as starting material.

1. Introduction. – Conformationally restricted α-amino acids **A** and **B** (*Scheme 1*) are useful tools for synthetic and medicinal chemists for the preparation of peptidomimetics, biologically active compounds, natural products, and organocatalysts [1]. (2-Carboxycyclopropyl)glycines **A** are of interest primarily as conformationally restricted analogs of glutamic acid, the major excitatory neurotransmitter in the central nervous system [2]. Proper choice of stereochemistry places the desired functional groups in such a way that the conformation of glutamate is fixed either in an extended or folded form [3], which allows the assessment of the spatial requirements for a wide range of ionotropic- (iGluRs) and metabotropic-glutamate receptors (mGluRs) [4], as well as different classes of transporters [5]. For example, **A** ($R^1 = H$, $R^2 = COOH$,

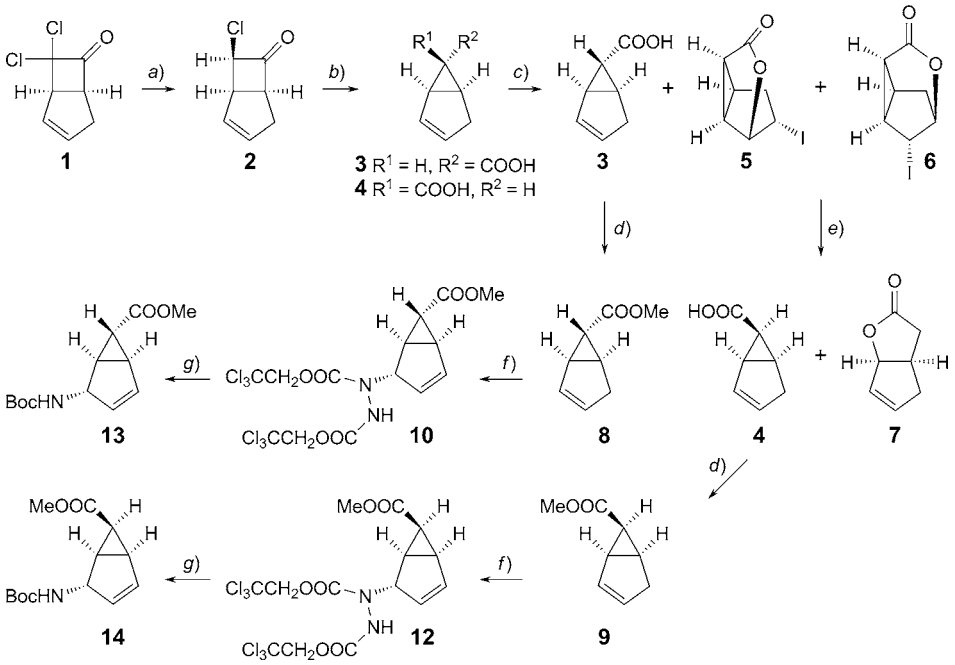
Scheme 1



DCG-IV) [6] is a potent $mGluR_2$ agonist, **A** ($R^1 = H$, $R^2 = MeOCH_2$, *trans*-MCG-IV) is a kainic acid agonist (iGluR), and **A** ($R^1 = MeOCH_2$, $R^2 = H$, *cis*-MCG-IV) is an *N*-methyl-D-aspartic agonist (iGluR) [7]. Proline derivatives **B** (R^2 or $R^1 = COOMe$) are members of the bicyclic amino acid family [8]. More specifically, they are a sub-class of proline-glutamic acid chimeras [9], in which backbone flexibility is restricted by the proline, and the conformation of the glutamate side chain is also locked, making them interesting building blocks for peptide synthesis [10]. Common precursors for the synthesis of **A** and **B** are the pyroglutamic acid derivatives **C** ($R^1 = H$, $R^2 = COOMe$; $R^1 = COOMe$, $R^2 = H$) [11], which by themselves are unique chiral synthons offering a wide variety of possible synthetic transformations [12]. Building block **C** ($R^1 = H$, $R^2 = COOMe$), synthezised from *Garner*'s aldehyde [13] in some 20 steps, is an intermediate in the first synthesis of DCG-IV (**17**) by *Ohfune* [6a] and is formed as a result of a spontaneous lactamization of the corresponding dicarboxylic amino acid **D**. To shorten the synthesis of the important building block **C**, we thought it should be possible to synthesize **D** from an amino substituted bicyclo[3.1.0]hex-2-ene derivative **E** by oxidative cleavage of the C=C bond. The γ-amino acid derivatives **E** ($R^1 = H$, $R^2 = COOMe$; $R^1 = COOMe$, $R^2 = H$) are conformationally restricted γ-amino butyric acid (GABA) analogs [14]. γ-Amino butyric acid, like glutamic acid, is present in the central nervous system [15], but in contrast to the latter, it acts through different receptors and transporters and functions as the major inhibitory neurotransmitter [16]. For the synthesis of building block **E**, we envisioned an allylic amination of methyl bicyclo[3.1.0]hex-2-en-6-carboxylates **F** as a possible route. In addition, these building blocks are interesting due to their relatively high level of saturation (Fsp^3) and number of stereogenic centers [17], making them attractive novel synthons in medicinal chemistry [18]. Herein, we report the synthesis of building blocks **E** ($R^1 = COOMe$, $R^2 = H$; $R^1 = H$, $R^2 = COOMe$) in racemic and optically active form, their conversions into pyroglutamate derivatives **C**, and the preparation of (2-carboxycyclopropyl)glycines **A**.

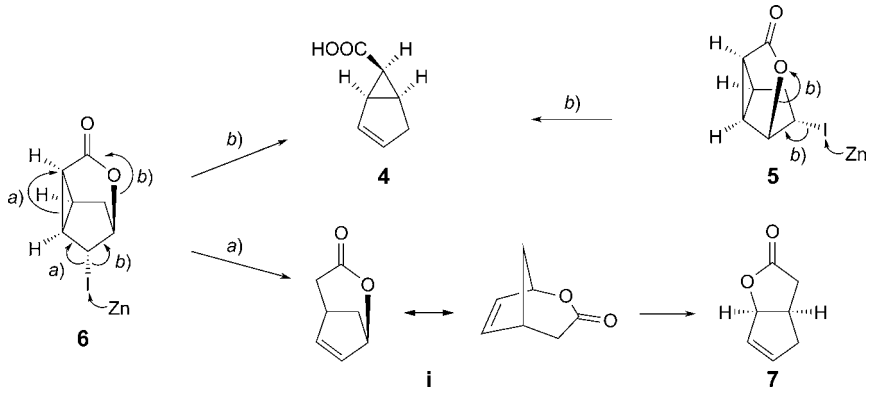
2. Results and Discussion. – 2.1. *Syntheses of* exo- *and* endo-*Methyl Bicyclo[3.1.0]-hex-2-ene-6-carboxylates* **8** *and* **9**. From the known syntheses of *exo*- and *endo*-bicyclo[3.1.0.]carboxylic acids **3** and **4** [19], we decided to follow the route described by *Brook et al.* [19c], because the starting material 7,7-dichlorobicylco[3.2.0]hept-2-en-6-one (**1**) is readily available in both enantiomeric forms [20], making the synthesis of our building blocks in homochiral form straightforward. To test and possibly refine our synthetic plan (*Scheme 2*), we first used commercially available racemic 7,7-dichlorobicylco[3.2.0]hept-2-en-6-one (**1**) as the starting material. Reduction with Zn in AcOH and distillation afforded the reported *endo*-chloroketone **2** [21], which then underwent a *Favorski* ring contraction upon treatment with KOH in dioxane/H_2O to produce a 6:4 mixture of *exo*- and *endo*-acid **3** and **4**, which were separated *via* iodolactonization [19a][19c]. Thus, treatment of this mixture with I_2/KI under basic conditions delivered γ-iodolactone **5** together with δ-iodolactone **6** in a ratio of 3:7 and *exo*-acid **3** [19a]. Subsequent treatment of these iodolactones with Zn under acidic conditions delivered not only the expected and already described *endo*-acid **4** (64%) [19a], but also a bicyclic lactone **7** (25%), which was identified by comparison of the ^{1}H- and ^{13}C-NMR, and IR spectra with those described in [22]. We hypothesized (*Scheme 3*) that the undesired

Scheme 2



a) Zn, AcOH [21]. *b*) KOH, Dioxane/H_2O [19c]. *c*) I_2, KI, $NaHCO_3$ [19a]. *d*) 2,2-Dimethoxypropane, TsOH, MeOH [24]. *e*) Zn, AcOH, THF [19a]. *f*) BTCEAD, $ClCH_2CH_2Cl$, 85°. *g*) Zn, AcOH, acetone, then MeOH, Et_3N, $(^tBoc)_2O$.

Scheme 3

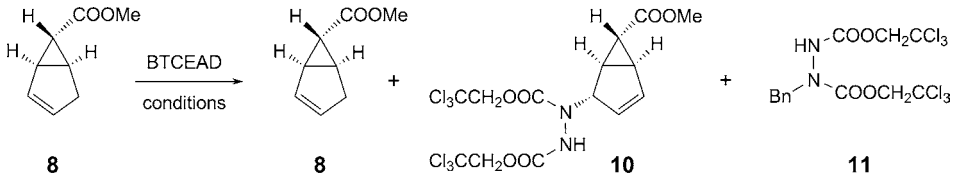


(in our case) bicylic lactone **7** stems from the δ-lactone **6**, since formation of a C=C bond and opening of the three-membered ring (*Path a*) is not possible from the γ-lactone **5**, whereas formation of a C=C bond and liberation of the *endo*-acid **4** (*Path b*)

is possible from both lactones. The so-formed bridged lactone **i** is not stable under these conditions and rearranges readily to lactone **7** [23]. To test this hypothesis, we separated the γ-iodolactone **5** from the δ-iodolactone **6** by column chromatography and subjected each iodolactone individually to the Zn reduction conditions. Indeed, whereas a mixture of *endo*-acid **4** (61%) and bicyclic lactone **7** (31%) was obtained when starting with **6**, only *endo*-acid **4** (86%) was formed using **5** as starting material. Esterification [24] of these two acids afforded then *exo*-ester **8** (81%) [25] and *endo*-ester **9** (93%) [26], respectively.

2.2. *Allylic Amination.* With *exo*- and *endo*-ester **8** and **9** in hand, we turned our attention to the allylic amination [27]. Of particular concern was the level of regio- and stereoselectivity, which we might achieve in this process. Since our synthesis plan called for a *trans* relationship between the newly introduced N-function and the three-membered ring and complete control of the regiochemistry (to avoid any racemization in the chiral series), we selected the method reported by *Leblanc et al.* [28], namely an allylic amination of olefins with bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD). Since the aza-ene reaction with olefins is thought to be a concerted, suprafacial process [29], and attack of the azodicarboxylate should occur from the less hindered side, we were confident of achieving the desired stereo- and regioselectivity. An additional advantage of that protocol are the mild conditions (Zn, AcOH, acetone) needed for the cleavage of the hydrazine to the amine. Besides the original procedure [28], which calls for running the reaction in benzene at different temperatures, two more variations are described in the literature: *i*) using different *Lewis* acids as catalysts in CH_2Cl_2 at room temperature [30], and *ii*) running the reaction 'on water' [31]. To find the best conditions for our case, we performed a short optimization with **8**, which is summarized in *Table 1*.

Table 1. *Allylic Amination*



8 **8** **10** **11**

BTCEAD = Bis(2,2,2-trichloroethyl) azodicarboxylate

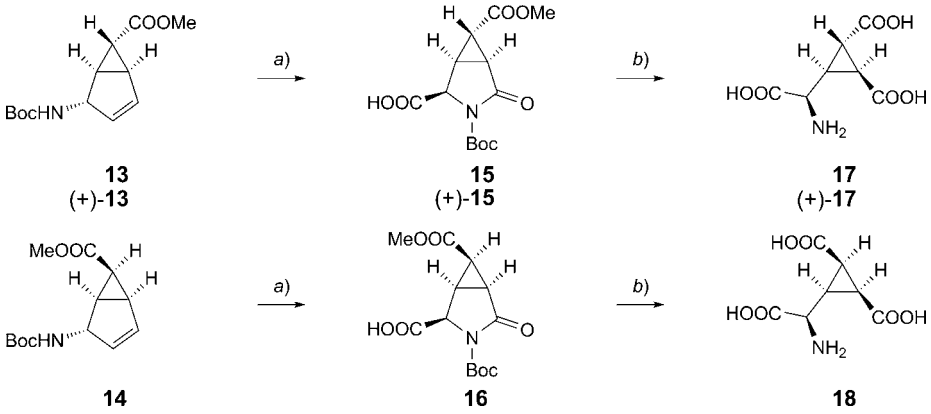
Entry	Solvent	Catalyst	Temp.	Time [h]	Yield [%][a])		
					8	**10**	**11**
1	Benzene	none	80°	16	11	77	–
2	Toluene	none	110°	16	–	84	14
3	CH_2Cl_2	none	r.t.	48	43	50	–
4	CH_2Cl_2	$(TfO)_2Cu$	r.t.	48	19	40	–
5	$ClCH_2CH_2Cl$	none	85°	16	–	93	–
6	H_2O	none	50°	10	–	83	–

[a]) Yield of isolated product.

Running the reaction in benzene for 16 h at reflux temperature (*Entry 1*) yielded **10** (77%) and starting material **8** (11%). Increasing the temperature to 110° by using toluene (*Entry 2*) drove the reaction to completion (84%), but **11** was formed as an additional product, which can be explained by an azo-ene reaction of toluene and BTCEAD. Comparing the results using the conditions of *Jorgenson et al.* [30] (*Entry 4*) *vs.* running the reaction in CH_2Cl_2 without catalyst at room temperature (*Entry 3*) led us to conclude not to use a *Lewis* acid as catalyst, but to use 1,2-dichloroethane as solvent and perform the reaction at 85° (*Entry 5*). We were pleased to see that the reaction was finished after 16 h and yielded **10** in 93% yield. To complete our small study, we also tested the protocol described by *Sharpless et al.* [31] (*Entry 6*). These conditions delivered **10** after 10 h in 83% yield. The drawback of this method was the formation of a white lump embedded with yellow particles, which contained not only **10** but also BTCEAD. To drive the reaction to completion, it was found necessary to break up this lump after 6 h and 8 h. Taking account of these findings, for the reaction of the *endo*-ester **9** with BTCEAD we also used 1,2-dichloroethane as solvent and employed a reaction temperature of 85°, which enabled **12** to be obtained in 79% yield after 16 h (*Scheme 1*). To obtain an orthogonally protected building block, the last step of the protocol in [28] was modified slightly. Instead of protecting the amine, which is released after reductive treatment (Zn, AcOH, acetone), as an acetate, we employed $(^t\text{Boc})_2\text{O}$ as an acylating reagent to afford Boc-protected **13** (74%) and **14** (80%), respectively. The expected *trans* relationship between H–C(4) and H–C(5) could not be unequivocally confirmed, since the coupling constant between these two H-atoms in the ^{1}H-NMR spectrum could not easily be determined. Although the width at half maximum of the corresponding signals indicated that the coupling constant values were rather small, suggesting a *trans* relationship as evidenced in [32], the final proof of the configuration stemmed from the preparation of *rac*-DCG-IV (**17**; *Scheme 4*). Improved *Sharpless* conditions [33] applied to **13** and **14** delivered pyroglutamate derivatives **15** (88%) and **16** (82%) after spontaneous lactamization [6a] of the initially formed dicarboxylic amino acid [34]. The ^{1}H-NMR coupling constants J(H–C(2),H–C(1)) = 6.0 Hz in **15** and J(H–C(2),H–C(1)) = 6.4 Hz in **16** were in agreement with a *cis* relationship as reported in [35]. This, together with the conversion of **15** into *rac*-DCG-IV **17** (80%) [6] by acidic hydrolysis, corroborated the stereochemical outcome of the azo-ene reaction. Applying the same conditions to **16** produced, for the first time, the all *cis*-substituted cyclopropyl glycine derivative **18** in 84% yield (*Scheme 4*).

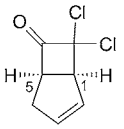
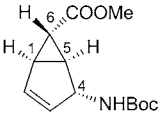
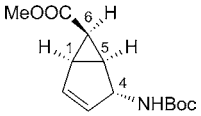
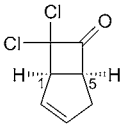
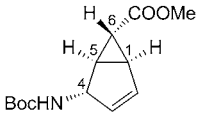
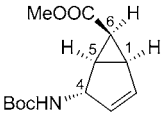
2.3. *Chiral Series.* For the synthesis of our chiral bicyclo[3.1.0]hex-2-ene building blocks, we modified our strategy in such a way that we decided not to separate the *endo*-acid **4** from the *exo*-acid **3** *via* iodolactonization, but to carry the mixture through the esterification and allylic amination steps and then isolate **13** and **14** as enantiomerically pure compounds by column chromatography. The results, using either (1*S*,5*R*)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one ((−)-**1**) [20] or the enantiomer (+)-**12** [20] as starting material, are shown in *Table 2*. The absolute configurations of these building blocks were initially deduced by assuming that the azo-ene reaction proceeds through a $[\pi 2_S + \pi 2_S + \sigma 2_S]$ process according to the *Woodward–Hoffmann* notation [36]. The absolute configurations were subsequently confirmed by the synthesis of (2*R*,2′*S*,3′*S*)-2-(2′,3′-dicarboxylcyclopropyl)glycine (*ent*-DCG IV) ((+)-**17**) $[\alpha]_D = +22.3$, (−)-**17** $[\alpha]_D = -20.2$ [6a]) from (+)-**13** by the reactions outlined above (*Scheme 4*).

Scheme 4



a) $NaIO_4$, $RuCl_3$, MeCN, CCl_4, H_2O. *b*) 10% HCl.

Table 2. *Chiral Building Blocks*

			
	(–)-**1**	(–)-**13**	(–)-**14**
$[\alpha]_D$	–89.8 (–81.0 [20])	–195.7	–375.8
Configuration	(1*S*,5*R*) [20]	(1*R*,4*R*,5*S*,6*S*)	(1*R*,4*R*,5*S*,6*R*)
Chiral HPLC	n.d.	8.29 (–)	10.31 (–)
			
	(+)-**1**	(+)-**13**	(+)-**14**
$[\alpha]_D$	+87.1 (+83.9 [20])	+181.5	+368.5
Configuration	(1*R*,5*S*) [20]	(1*S*,4*S*,5*R*,6*R*)	(1*S*,4*S*,5*R*,6*S*)
Chiral HPLC	n.d.	10.60 (+)	9.79 (+)

3. Conclusions. – In summary, we have developed a concise and fully stereocontrolled synthesis of the novel, chiral, bifunctional bicyclo[3.1.0]hex-2-ene building blocks **13** and **14**. These building blocks provide not only a short access to (2,3-dicarboxycyclopropyl)glycines **17** and **18**, but should also allow straightforward modification of the substituents at the 2 or 3 position of the three-membered ring. Additionally, together with the highly functionalized pyroglutamate derivatives **15** and **16**, they might be versatile building blocks in medicinal chemistry due to their chirality and three-dimensional shape.

We thank the Analytical Departments of the *Roche Innovation Center Basel* for skillful measurement of NMR, IR, MS, ORD, and chiral HPLC data. The careful reading of the manuscript by Dr. *Roger Norcross* is gratefully acknowledged.

Experimental Part

General. All solvents and reagents were used from commercial sources without further purification or prepared as described in the literature. Thin-layer chromatography (TLC): *EMD* pre-coated silica gel *60* F_{254} glass plates; visualization with UV light (254 nm) or chemical detection ($(NH_4)_2Ce(MoO_4)_3$ soln. or $KMnO_4$ soln.). Flash chromatography (FC): silica gel *60* (*Merck*, 230–400 mesh), with the eluent mixtures given for the corresponding procedures. Enantiomeric purities: chiral HPLC with an *Ultimate 3000* coupled with a *Chiralizer* (*IBZ Messtechnik*). Optical rotations (ORD): *Anton Parr MCP 500* at 20°. M.p.: *Büchi B-540* instrument; uncorrected. FT-IR (solid state (ATR)): *Nicolet i5S* instrument; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker Avance II 300* or a *Bruker Avance III 600* spectrometer, in $CDCl_3$, (D_6)DMSO or D_2O; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Applied Biosystem API300*; in *m*/*z*. HR-LC/MS: *Agilent Q-TOF 6520* system; in *m*/*z*. Elemental analyses: *Solvias AG* (Mattenstrasse, Postfach, CH-4002 Basel, Switzerland).

*(1*RS*,5*SR*,6*SR*)-Bicyclo[3.1.0]hex-2-ene-6-carboxylic Acid* (**4**) *and (3a*RS*,6a*SR*)-3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-one* (**7**). To a soln. of a mixture (3:7) of iodolactones **5** and **6** [19a][19c] (7.50 g, 30 mmol) in THF (50 ml), AcOH (1.5 ml), and H_2O (1.5 ml) was added Zn (3.3 g, 58.5 mmol) in small portions at 0° (ice/water bath). Then, the ice/water bath was removed, and the mixture was stirred for 1.5 h at ambient temp. After filtration through a pad of *Celite*, the filtrate was partially concentrated, diluted with H_2O (75 ml), and acidified with 25% HCl to pH = 1. The aq. layer was extracted with Et_2O (3 × 80 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated to give 3.48 g of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **7** (0.94 g, 25%) as colorless oil (IR, ^1H- and ^{13}C-NMR spectra as described in [22]) and **4** (2.41 g, 64%) as colorless solid. M.p. 88–91° (90–91° [19a]).

Separation of exo-*8-Iodo-2-oxatricyclo[3.3.0.0^{4,6}]octan-3-one* (**5**) *and* exo-*6-Iodo-4-oxatricyclo[3.2.1.0^{2,7}]octan-3-one* (**6**). A mixture of the iodolactones **5** and **6** (4.81 g, 19.2 mmol) was separated by FC (heptane/AcOEt 4:1) to afford **5** (1.25 g; R_f (heptane/AcOEt 4:1) 0.37) and **6** (3.38 g; R_f (heptane/AcOEt 4:1) 0.24).

Data of **5**. M.p. 120.6–121.4° (cyclohexane). IR (ATR): 2914*w*, 2857*w*, 1758*s*, 1440*m*, 1360*m*, 1342*m*, 1320*s*, 1301*m*, 1276*m*, 1258*w*, 1209*m*, 1194*m*, 1030*s*, 1045*m*, 1005*s*, 991*s*, 964*s*, 920*s*, 897*m*, 868*m*, 824*s*, 798*s*, 783*m*, 667*m*, 619*m*, 591*s*. ^1H-NMR (600 MHz, $CDCl_3$): 5.08 (br. *d*, *J* = 4.2, H–C(1)); 4.29 (br. *d*, *J* = 4.7, H–C(8)); 3.37 (*td*, *J* = 6.1, 4.2, H–C(5)); 2.69 (*ddd*, *J* = 16.3, 6.4, 1.4, H–C(7)); 2.52 (*ddd*, *J* = 16.3, 4.7, 1.6, H–C(7)); 2.31 (*ddd*, *J* = 8.4, 6.1, 1.5, H–C(4)); 2.22 (*ddd*, *J* = 8.4, 6.1, 1.6, H–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 174.1 (C(3)); 87.9 (C(1)); 35.8, 34.4, 34.0 (C(5,7,8)); 29.2 (C(4)); 27.1 (C(6)). GC/EI-MS: 250 (M^+), 123 ($[M-I]^+$), 79 ($[M-I-CO_2]^+$). Anal. calc. for $C_7H_7IO_2$ (250.03): C 33.63, H 2.82, I 50.75; found C 33.48, H 2.96, I 50.67.

Data of **6**. M.p. 114.6–115.1° (cylohexane). IR (ATR): 2978*w*, 2949*w*, 2858*w*, 1723*s*, 1711*s*, 1436*w*, 1374*m*, 1354*m*, 1329*m*, 1318*w*, 1275*w*, 1254*w*, 1210*s*, 1183*w*, 1160*m*, 1147*m*, 1096*m*, 1085*m*, 1025*s*, 987*s*, 967*s*, 952*s*, 924*m*, 886*m*, 854*m*, 838*m*, 809*s*, 783*m*, 762*m*, 713*m*, 649*m*, 598*s*. ^1H-NMR (600 MHz, $CDCl_3$): 4.69–4.67 (*m*, H–C(5)); 4.14 (br. *s*, H–C(6)); 2.68 (*dt*, *J* = 13.7, 3.0, H–C(8); 2.56–2.53 (*m*, H–C(7)); 2.32–2.28 (*m*, H–C(1)); 2.00 (*td*, *J* = 7.5, 0.8, H–C(2)); 1.93 (*dd*, *J* = 17.7, 0.7, H–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.3 (C(3)); 79.0 (C(5)); 27.7, 26.6 (C(1,7)); 25.6 (C(2)); 21.6, 20.1 (C(6,8)). GC/EI-MS: 250 (M^+), 123 ($[M-I]^+$), 79 ($[M-I-CO_2]^+$). Anal. calc. for $C_7H_7IO_2$ (250.03): C 33.63, H 2.82, I 50.75; found C 33.57, H 2.97, I 50.55.

*(1*RS*,5*SR*,6*SR*)-Bicyclo[3.1.0]hex-2-ene-6-carboxylic Acid* (**4**) *and (3a*RS*,6a*SR*)-3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-one* (**7**). To a soln. of δ-iodolactone **6** (2.50 g, 10 mmol) in THF (16 ml), AcOH (0.5 ml), and H_2O (0.5 ml) was added Zn (1.1 g, 19.5 mmol) in small portions at 0° (ice/water bath). Then, the ice/water bath was removed, and the mixture was stirred for 1.5 h at ambient temp. After filtration through a pad of *Celite*, the filtrate was partially concentrated, diluted with H_2O (25 ml), and

acidified with 25% HCl to pH = 1. The aq. layer was extracted with Et_2O (3 × 50 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated to give 1.24 g of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **7** (0.38 g, 31%) and **4** (0.76 g, 61%).

*(1*RS*,5*SR*,6*SR*)-Bicyclo[3.1.0]hex-2-ene-6-carboxylic Acid* (**4**). To a soln. of γ-iodolactone **5** (1.0 g, 4 mmol) in THF (10 ml), AcOH (0.3 ml), and H_2O (0.3 ml) was added Zn (0.51 g, 7.8 mmol) in small portions at 0° (ice/water bath). Then, the ice/water bath was removed, and the mixture was stirred for 1.5 h at ambient temp. After filtration through a pad of *Celite*, the filtrate was partially concentrated, diluted with H_2O (10 ml), and acidified with 25% HCl to pH = 1. The aq. layer was extracted with Et_2O (3 × 30 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated to give **4** (0.43 g, 86%).

*Methyl (1*RS*,5*SR*,6*RS*)-Bicyclo[3.1.0]hex-2-ene-6-carboxylate* (**8**). To a soln. of **3** [19c] (8.69 g, 70 mmol) in MeOH (300 ml) and 2,2-dimethoxypropane (100 ml) was added TsOH (3.34 g, 17.6 mmol), and the mixture was stirred for 24 h at ambient temp. The soln. was partly concentrated, then H_2O (200 ml) and Et_2O (200 ml) were added. The layers were separated, and the aq. phase was extracted with Et_2O (2 × 200 ml). The combined org. layers were washed with 0.5N NaOH (200 ml), H_2O (200 ml), and brine (200 ml), then dried (Na_2SO_4), and evaporated to give light-yellow oil (8.61 g), which was distilled (Kugelrohr, 75–80°, 0.5 Torr) to yield **8** (7.98 g, 81%). ^{1}H-NMR Spectrum as described in [24].

*Methyl (1*RS*,5*SR*,6*SR*)-Bicyclo[3.1.0]hex-2-ene-6-carboxylate* (**9**). To a soln. of **4** (2.48 g, 20 mmol) in MeOH (100 ml) and 2,2-dimethoxypropane (30 ml) was added TsOH (0.95 g, 5 mmol), and the soln. was stirred for 24 h at 40°. The soln. was partly concentrated, then H_2O (120 ml) and Et_2O (120 ml) were added. The layers were separated, and the aq. phase was extracted with Et_2O (2 × 120 ml). The combined org. layers were washed with 0.5N NaOH (120 ml), H_2O (120 ml), and brine (120 ml), then dried (Na_2SO_4) and evaporated to give light-yellow oil (2.89 g), which was distilled (Kugelrohr, 75–80°, 0.5 Torr) to yield **9** (2.58 g, 93%). ^{1}H-NMR Spectrum as described in [25][26].

*Bis(2,2,2-trichloroethyl) 1-[(1*RS*,2*SR*,5*SR*,6*RS*)-6-(Methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]-hydrazine-1,2-dicarboxylate* (**10**). *i*) In benzene: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in benzene (25 ml) was heated for 16 h at 85° (oil bath). The soln. was concentrated, and the residue (2.64 g) was purified by FC (heptane/AcOEt 10:1) to yield **8** (78 mg, 11%) as colorless oil and **10** (2.01 g, 77%) as light-yellow foam.

Data of **10**. IR (ATR): 3310*s*, 3080*w*, 3069*w*, 3062*w*, 3001*m*, 2925*s*, 2854*s*, 1768*s*, 1731*s*, 1704*s*, 1503*m*, 1445*s*, 1403*s*, 1365*m*, 1347*w*, 1289*s*, 1253*s*, 1201*s*, 1179*s*, 1144*s*, 1106*m*, 1082*w*, 1058*m*, 1044*m*, 1024*w*, 981*w*, 963*w*, 918*w*, 897*w*, 853*m*, 820*s*, 791*s*, 754*s*, 711*s*, 650*m*, 606*w*, 570*s*. ^{1}H-NMR (600 MHz, (D_6)DMSO, 120°): 9.65 (br. *s*, NH); 6.20 (br. *d*, *J* = 5.1, H–C(4′)); 5.52–5.41 (*m*, H–C(3′)); 5.09–5.07 (*m*, H–C(2′)); 4.86 (*s*, CH_2O); 4.79 (br. *s*, CH_2O); 3.59 (*s*, MeO), 2.51–2.47, 2.45–2.38 (2*m*, H–C(1′,5′)); 1.03 (*t*, *J* = 2.9, H–C(6′)). ESI-MS: 515 ($[M-H]^-$).

ii) In toluene: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in toluene (25 ml) was heated for 16 h at 110° (oil bath). The soln. was concentrated, and the residue (2.76 g) was purified by FC (heptane/AcOEt 4:1) to yield *bis(2,2,2-trichloroethyl) 1-benzylhydrazine-1,2-dicarboxylate* (**11**; 0.34 g, 14%) as light-yellow solid and **10** (2.18 g, 84%) as light-yellow foam.

Data of **11**. ^{1}H-NMR (600 MHz, (D_6)DMSO, 120°): 9.88 (br. *s*, NH); 7.36–7.24 (*m*, 5 arom. H); 4.86, 4.78, 4.68 (3*s*, 2 × CH_2O, CH_2N). ESI-MS: 469 ($[M-H]^-$).

iii) In CH_2Cl_2: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in CH_2Cl_2 (25 ml) was stirred for 48 h at ambient temp. The soln. was concentrated, and the residue (2.86 g) was purified by FC (heptane/AcOEt 10:1) to yield **8** (298 mg, 43%) as colorless oil and **10** (1.31 g, 50%) as light-yellow foam.

iv) In CH_2Cl_2 with $(TfO)_2Cu$: To a soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in CH_2Cl_2 (25 ml) was added $(TfO)_2Cu$ (362 mg, 1 mmol), and the mixture was stirred for 48 h at ambient temp. The soln. was concentrated, and the residue (3.12 g) was purified by FC (heptane/AcOEt 10:1) to yield **8** (132 mg, 19%) as colorless oil and **10** (1.06 g, 40%) as light-yellow foam.

v) In $ClCH_2CH_2Cl$: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in $ClCH_2CH_2Cl$ (25 ml) was stirred for 16 h at 85° (oil bath). The soln. was concentrated,

and the residue (2.88 g) was purified by FC (heptane/AcOEt 10:1) to yield **10** (2.42 g, 93%) as light-yellow foam.

vi) 'On water': To a suspension of bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in H_2O (25 ml) was added **8** (691 mg, 5 mmol), and the mixture was stirred for 6 h at 50° (oil bath). A light-yellow lump formed and was broken up, and the suspension was stirred for another 2 h. The same procedure was repeated, and the suspension was stirred for another 2 h. The mixture was cooled, and the suspension was extracted with AcOEt (2 × 80 ml). The combined org. layers were dried (Na_2SO_4) and evaporated to give 2.67 g of crude product, which was purified by FC (heptane/AcOEt 10:1) to yield **10** (2.16 g, 83%) as light-yellow foam.

*Bis(2,2,2-trichloroethyl) 1-[(1*RS*,2*SR*,5*SR*,6*SR*)-6-(Methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]-hydrazine-1,2-dicarboxylate* (**12**). A soln. of **9** (2.07 g, 15 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (6.85 g, 18 mmol) in $ClCH_2CH_2Cl$ (75 ml) was stirred for 16 h at 85° (oil bath). The soln. was concentrated, and the residue (7.37 g) was purified by FC (heptane/AcOEt 10:1) to yield **12** (6.21 g, 79%) as light-yellow foam. ^{1}H-NMR (600 MHz, (D_6)DMSO, 120°): 9.62 (br. *s*, NH); 5.89 (br. *d*, *J* = 5.5, H–C(4′)); 5.56 (br. *s*, H–C(2′)); 5.42–5.39 (*m*, H–C(3′)); 4.86 (*s*, CH_2O); 4.79 (br. *s*, CH_2O); 3.50 (*s*, MeO); 2.47–2.45 (*m*, 1 H) and 2.21–2.18 (*m*, 2 H) (H–C(1′,5′,6′)). ESI-MS: 515 ([*M* − H]$^-$).

*Methyl (1*RS*,4*RS*,5*SR*,6*SR*)-4-[(*tert-*Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate* (**13**). To a soln. of **10** (1.56 g, 3 mmol) in THF (13.5 ml), acetone (1.5 ml), and AcOH (3 ml) was added Zn (4.68 g, 71.5 mmol) in small portions over 30 min. After 2 h, the mixture was filtered, and the soln. was concentrated. MeOH (15 ml) and Et_3N (1.38 ml, 9.9 mmol) were added, and the soln. was cooled to 0°. After addition of (^{t}Boc)$_2$O (720 mg, 3.3 mmol), the mixture was stirred for 5 h at ambient temp. The soln. was concentrated, and the residue was dissolved in CH_2Cl_2 (50 ml). The org. phase was washed with sat. NH_4Cl soln. (2 × 35 ml) and H_2O (35 ml), dried (Na_2SO_4) and concentrated to give 689 mg of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **13** (563 mg 74%) as colorless oil, which solidified on standing. An anal. sample was recrystallized (AcOEt, hexane). R_f (heptane/AcOEt 4:1) 0.41. M.p. 79.9–80.5°. IR (ATR): 3355*m*, 3078*w*, 3055*w*, 2977*w*, 2933*w*, 1724*m*, 1680*s*, 1677*s*, 1505*m*, 1457*w*, 1435*m*, 1389*w*, 1366*m*, 1328*w*, 1321*w*, 1264*m*, 1254*m*, 1237*m*, 1172*s*, 1078*w*, 1046*m*, 1028*m*, 992*w*, 961*w*, 951*w*, 933*w*, 865*m*, 853*w*, 829*w*, 801*w*, 789*w*, 762*w*, 748*w*, 716*w*, 703*w*, 695*w*, 647*w*, 610*w*, 579*w*, 552*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): 6.11 (*dddd*, *J* = 5.5, 2.2, 1.3, 0.7, H–C(2)); 5.50 (*ddd*, *J* = 5.5, 1.8, 1.6, H–C(3)); 4.64–4.51 (*m*, H–C(4)), NH); 3.66 (*s*, MeO); 2.46 (*dq*, *J* = 6, 2.2, H–C(1)); 2.30–2.25 (*m*, H–C(5)); 1.46 (*s*, Me_3C); 1.16 (br. *dd*, *J* = 3.2, 2.2, H–C(6)). ^{13}C-NMR (150 MHz, $CDCl_3$): 171.6 (*C*OOMe); 154.8 (N*C*OOC); 135.4 (C(2)); 130.2 (C(3)); 79.8 (NCOO*C*)); 57.2 (C(4)); 51.8 (MeO); 33.5, 33.1, 32.1 (C(1,5,6)); 28.4 (*Me*$_3$C). ISP-MS: 270.9 ([*M* + NH_4]$^+$), 254.0 ([*M* + H]$^+$). Anal. calc. for $C_{13}H_{19}NO_4$ (253.30): C 61.64, H 7.56, N 5.53; found C 61.66, H 7.50, N 5.55. Chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90:10, flow rate 1 ml/min, t_R 8.00 min (−), t_R 10.40 min (+).

*Methyl (1*RS*,4*RS*,5*SR*,6*RS*)-4-[(*tert-*Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate* (**14**). To a soln. of **12** (5.19 g, 10 mmol) in THF (45 ml), acetone (5 ml), and AcOH (10 ml) was added Zn (15.6 g, 23.9 mmol) in small portions over 45 min. After 6 h, the mixture was filtered, and the soln. was concentrated. MeOH (50 ml) and Et_3N (4.6 ml, 33 mmol) were added, and the soln. was cooled to 0°. After addition of (^{t}Boc)$_2$O (2.40 g, 11 mmol), the mixture was stirred for 5 h at ambient temp. The soln. was concentrated, and the residue was dissolved in CH_2Cl_2 (200 ml). The org. phase was washed with sat. NH_4Cl soln. (2 × 150 ml) and H_2O (150 ml), dried (Na_2SO_4) and concentrated to give 2.46 g of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **14** (2.05 mg, 80%) as colorless oil, which solidified on standing. An anal. sample was recrystallized (AcOEt, hexane). R_f (AcOEt/heptane 1:4) 0.24. M.p. 98.5–99.0°. IR (ATR): 3323*w*, 2980*w*, 2928*w*, 1724*s*, 1689*s*, 1521*s*, 1438*m*, 1386*w*, 1365*m*, 1300*s*, 1275*w*, 1263*m*, 1244*w*, 1206*w*, 1164*s*, 1148*s*, 1219*s*, 1084*m*, 1061*m*, 1041*m*, 1023*m*, 973*m*, 962*m*, 938*w*, 885*m*, 866*w*, 824*w*, 812*w*, 793*w*, 768*w*, 746*m*, 663*m*. ^{1}H-NMR (600 MHz, $CDCl_3$): 5.84 (br. *d*, *J* = 5.5, H–C(2)); 5.68 (*dtd*, *J* = 5.5, 1.8, 0.6, H–C(3)); 4.93 (br. *d*, *J* = 7.6, H–C(4)); 4.51 (br. *d*, *J* = 7.6, NH); 3.58 (*s*, MeO), 2.45 (*ddt*, *J* = 8, 5.6, 2.4, H–C(1)); 2.08 (*tdd*, *J* = 8.0, 0.7, 0.6, H–C(6)); 1.98 (br. *dd*, *J* = 8.0, 5.6, H–C(5)); 1.46 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.2 (*C*OOMe); 154.8 (N*C*OOC); 132.3, 130.6 (C(2,3)); 79.6 (Me_3C); 55.1 (CN); 51.5 (MeO); 30.3, 29.6, 28.7 (C(1,5,6)); 28.4 (*Me*$_3$C). ISP-MS: 270.1 ([*M* + NH_4]$^+$), 254.1 ([*M* + H]$^+$). Anal. calc. for $C_{13}H_{19}NO_4$ (253.30): C 61.64, H 7.56, N 5.53; found C 61.41,

H 7.25, N 5.44. Chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90:10, flow rate 1 ml/min, t_R 10.00 min (+), t_R 10.49 min (−).

*(1*RS*,2*RS*,5*SR*,6*SR*)-3-(*tert*-Butoxycarbonyl)-6-(methoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid* (**15**). To a soln. of **13** (1.01 g, 4 mmol) in a mixture of MeCN (12 ml), CCl_4 (12 ml), and H_2O (18 ml) was added $NaIO_4$ (3.51 g, 16.4 mmol) followed by $RuCl_3$ (18.3 mg, 0.088 mmol) at ambient temp. After stirring for 4 h, the mixture was diluted with CH_2Cl_2 (25 ml) and H_2O (10 ml). The phases were separated, and the aq. phase was extracted with CH_2Cl_2 (2 × 20 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated to give 1.06 g of light-red foam, which was purified by FC (AcOEt/AcOH 95:5) to give **15** (1.0 g, 88%) as white foam. An anal. sample was crystallized from AcOEt. M.p. 126.5–127.3°. IR (ATR): 3457*w*, 3188*w* (br.), 3086*w*, 2923*s*, 2853*s*, 2728*w*, 2614*w*, 1788*s*, 1730*s*, 1497*w*, 1396*w*, 1373*w*, 1306*m*, 1256*m*, 1150*m*, 1086*m*, 1058*m*, 1016*m*, 945*w*, 906*w*, 879*w*, 846*w*, 814*w*, 763*w*, 738*w*, 673*w*, 618*w*, 585*w*. ^{1}H-NMR (600 MHz, $CDCl_3$): 6.75 (br. *s*, COOH); 4.81 (*d*, *J* = 6.0, H–C(2)); 3.72 (*s*, MeO); 2.70 (*ddd*, *J* = 6.6, 6.0, 2.8, H–C(1)); 2.59 (*dd*, *J* = 6.6, 2.8, H–C(5)); 2.40 (*t*, *J* = 2.8, H–C(6)); 1.47 (*s*, Me_3C). ^{13}C-NMR (150 MHz, $CDCl_3$): 172.9, 169.6, 169.0 (C(4), *C*OOMe, COOH)); 148.9 (NCO); 84.6 (Me_3C), 58.2 (C(2)); 52.7 (MeO)); 29.3 (C(5)); 27.6 (*Me*$_3$C); 22.0, 21.9 (C(1,6)). ISP-MS: 301.4 ($[M+H]^+$). Anal. calc. for $C_{13}H_{17}NO_7$ (299.28): C 52.17, H 5.73, N 4.68; found C 51.74, H 5.76, N 4.63.

*(1*RS*,2*RS*,5*SR*,6*RS*)-3-(*tert*-Butoxycarbonyl)-6-(methoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid* (**16**). To a soln. of **14** (507 mg, 2 mmol) in a mixture of MeCN (6 ml), CCl_4 (6 ml), and H_2O (9 ml) was added $NaIO_4$ (1.75 g, 8.2 mmol), followed by $RuCl_3$ (9.92 mg, 0.044 mmol) at ambient temp. After stirring for 4 h, the mixture was diluted with CH_2Cl_2 (15 ml) and H_2O (5 ml). The phases were separated, and the aq. phase was extracted with CH_2Cl_2 (2 × 15 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated to give 581 mg of light-red foam, which was separated by FC (AcOEt/AcOH 95:5) to yield **16** as white foam (491 mg, 82%). An anal. sample was crystallized from AcOEt. M.p. 144.1–146.2°. IR (ATR): 3276*w* (br.), 2967*w*, 1780*s*, 1752*s*, 1731*m*, 1685*m*, 1476*w*, 1435*w*, 1395*w*, 1369*w*, 1350*m*, 1336*m*, 1314*m*, 1301*m*, 1254*w*, 1211*s*, 1151*s*, 1093*w*, 1076*m*, 1054*w*, 1016*m*, 984*m*, 957*m*, 944*s*, 918*w*, 869*w*, 854*m*, 835*w*, 824*m*, 779*m*, 763*w*, 734*w*, 694*m*. ^{1}H-NMR (600 MHz, $CDCl_3$): 4.92 (*d*, *J* = 6.4, H–C(2)); 3.71 (*s*, MeO); 2.74 (br. *s*, COOH); 2.59 (*dt*, *J* = 8.6, 6.4, H–C(1)); 2.53 (*dd*, *J* = 8.6, 6.4, H–C(5)); 2.25 (*t*, *J* = 8.6, H–C(6)); 1.49 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$/(D_6)DMSO (1 drop)): 169.2, 169.0, 167.0 (C(4), *C*OOMe, COOH); 147.9 (NCO); 82.5 (Me_3C); 57.5 (C(2)); 51.7 (MeO); 27.3 (*Me*$_3$C); 26.0, 24.7 (C(5,6)); 21.4 (C(1)). ISP-MS: 300.11 ($[M+H]^+$). Anal. calc. for $C_{13}H_{17}NO_7$ (299.28): C 52.17, H 5.73, N 4.68; found C 51.79, H 5.61, N 4.60.

*(1*RS*,2*RS*)-3-[(SR)-Amino(carboxy)methyl]cyclopropane-1,2-dicarboxylic Acid* (**17**). A soln. of **15** (299 mg, 1 mmol) in 10% HCl (10 ml) was heated at 100° (oil bath) for 3 h. The soln. was cooled to r.t. and concentrated to give 281 mg of crude product, which was submitted to ion exchange chromatography (*Dowex 50WX4*, elution with 12.5% $NH_3 \cdot H_2O$) to give **17** (205 mg, 86%) as white, hygroscopic foam (diammonium salt). ^{1}H-NMR (600 MHz, D_2O): 3.95 (*d*, *J* = 9.9, H–C(2′)); 2.09 (*dd*, *J* = 9.5, 5.0, H–C(3)); 1.98 (*dd*, *J* = 5.6, 5.0, H–C(2)); 1.83 (*ddd*, *J* = 9.9, 9.5, 5.6, H–C(1)). ^{13}C-NMR (150 MHz, D_2O): 178.8, 177.1, 173.5 (3 CO); 52.2 (C(2′)); 29.5, 28.4, 26.9 (C(1,2,3)). LC/HR-MS: 203.0439 ($C_7H_9NO_6^+$; calc. 203.0429).

*(1*RS*,2*SR*,3*rs*)-3-[(*RS*)-Amino(carboxy)methyl]cyclopropane-1,2-dicarboxylic Acid* (**18**). A soln. of **16** (213 mg, 0.71 mmol) in 10% HCl (8 ml) was heated at 100° (oil bath) for 3 h. The soln. was cooled to r.t. and concentrated to give 253 mg of crude product, which was submitted to ion exchange chromatography (*Dowex 50WX4*, elution with 12.5% $NH_3 \cdot H_2O$) to give **18** (143 mg, 84%) as white, hygroscopic foam (diammonium salt). ^{1}H-NMR (600 MHz, D_2O): 4.44 (*d*, *J* = 10.9, H–C(2′)); 2.17–2.08 (*m*, H–C(1,2)); 1.64 (*dt*, *J* = 10.9, 8.7, H–C(3)). ^{13}C-NMR (150 MHz, D_2O): 176.1, 175.8, 174.6 (3 CO), 51.1 (C(2′)), 29.5, 28.4, 26.9 (C(1,2,3)). LC/HR-MS: 203.0448 ($C_7H_9NO_6^+$; calc. 203.0429).

*Methyl (1*R*,4*R*,5*S*,6*S*)-4-[(*tert*-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate* ((−)-**13**) *and Methyl (1*R*,4*R*,5*S*,6*R*)-4-[(*tert*-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate* ((−)-**14**). To a soln. of (1*S*,5*R*)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one ((−)-**1**; 4.43 g, 25 mmol; $[\alpha]_D = -89.8$ (*c* = 1 in $CHCl_3$) ($[\alpha]_D = -81.0$ (*c* = 0.75 in $CHCl_3$) [20]) in AcOH (125 ml) was added with stirring and cooling Zn (1.64 g, 25 mmol) in small portions over a period of 30 min. The soln. was diluted with H_2O (150 ml) and extracted with AcOEt (3 × 120 ml). The org. layer was washed with H_2O

(200 ml), sat. $NaHCO_3$ soln. (2 × 200 ml), dried (Na_2SO_4), and concentrated to give a mixture (92 : 8) of (1*S*,5*R*,7*S*)-7-chlorobicylo[3.2.0]hept-2-en-6-one and (1*S*,5*R*,7*R*)-7-chlorobicylo[3.2.0]hept-2-en-6-one (3.56 g, 97%) as light-yellow oil, which was used for the next step without further purification.

A mixture (92 : 8) of (1*S*,5*R*,7*S*)-7-chlorobicylo[3.2.0]hept-2-en-6-one and (1*S*,5*R*,7*R*)-7-chlorobicylo[3.2.0]hept-2-en-6-one (3.46 g, 24.3 mmol) was added dropwise to a soln. of KOH (9.53 g, 170 mmol) in a mixture of H_2O (105 ml) and dioxane (45 ml) at ambient temp. After 30 min, the soln. was acidified to pH = 1 with 25% HCl. The aq. phase was extracted with CH_2Cl_2 (3 × 100 ml), dried (Na_2SO_4), and concentrated to give a 3 : 1 mixture (H–C(2) signal in ^{1}H-NMR spectrum) of (1*S*,5*R*,6*S*)-bicyclo[3.1.0]-hex-2-ene-6-carboxylate and (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (2.85 g, 94%) as white solid, which was used directly for the next step.

To a soln. of a mixture (3 : 1) of (1*S*,5*R*,6*S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate and (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (2.85 g, 23 mmol) in MeOH (100 ml) and 2,2-dimethoxypropane (35 ml) was added TsOH (1.09 g, 5.74 mmol), and the soln. was stirred for 24 h at 40°. The soln. was partly concentrated, then H_2O (80 ml) and Et_2O (80 ml) were added. The layers were separated, and the aq. phase was extracted with Et_2O (80 ml). The combined org. layers were washed with 0.5N NaOH (80 ml), H_2O (80 ml), and brine (80 ml), dried ($NaSO_4$), and evaporated to give light-yellow oil (2.84 g), which was distilled (Kugelrohr, 75–80°, 0.5 Torr) to yield a 3 : 1 mixture (MeO signal in ^{1}H-NMR-spectrum) of methyl (1*S*,5*R*,6*S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate and methyl (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate as colorless oil (2.41 g, 76%).

A soln. of methyl (1*S*,5*R*,6*S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate and methyl (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (3 : 1) (2.07 g, 15 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (6.85 g, 18 mmol) in $ClCH_2CH_2Cl$ (75 ml) was stirred at 85° (oil bath) for 16 h. The mixture was concentrated, and the residue was purified by FC (heptane/AcOEt 4 : 1) to give bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*S*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate and bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*R*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate (6.18 g, 79%; 3 : 1) as colorless foam.

To a soln. of bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*S*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate and bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*R*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate (3 : 1 mixture) (3.11 g, 6 mmol) in THF (27 ml), acetone (3 ml) and AcOH (6 ml) was added Zn (9.33 g, 143 mmol) in small portions over 30 min. After 5 h, the mixture was filtered, and the soln. was concentrated. MeOH (30 ml) and Et_3N (2.76 ml, 19.8 mmol) were added, and the soln. was cooled to 0°. After addition of (^{t}Boc)$_2$O (1.44 g, 6.6 mmol), the mixture was stirred for 5 h at ambient temp. The soln. was concentrated, and the residue was dissolved in CH_2Cl_2. The org. phase was washed with sat. NH_4Cl soln. (2 × 60 ml) and H_2O (60 ml), dried (Na_2SO_4), and concentrated to give 1.29 g of crude product, which was purified by FC (heptane/AcOEt 4 : 1) and crystallized (AcOEt, hexane) to give (−)-**13** (0.89 g, 59%) as colorless needles, R_f (heptane/AcOEt 4 : 1) 0.39. ^{1}H-NMR spectrum identical to **13**. M.p. 84.4–85.1°, $[\alpha]_D = -195.7$ ($c = 1$ in $CHCl_3$), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, t_R 8.29 min (−) and (−)-**14** (0.23 g, 15%) as colorless needles. R_f (heptane/AcOEt 4 : 1) 0.24. ^{1}H-NMR spectrum identical to **14**. M.p. 92.6–93.0°, $[\alpha]_D = -375.8$ ($c = 1$ in $CHCl_3$), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, t_R 10.31 min (−).

*Methyl (1*S*,4*S*,5*R*,6*R*)-4-[(*tert*-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate* ((+)-**13**) *and Methyl (1*S*,4*S*,5*R*,6*S*)-4-[(*tert*-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate* ((+)-**14**). Using the same sequence as above but starting with (1*R*,5*S*)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one ($[\alpha]_D = +87.1$ ($c = 1$ in $CHCl_3$) ($[\alpha]_D = +83.9$ ($c = 0.75$ in $CHCl_3$) [20]) afforded (+)-**13** (1.46 g), R_f (heptane/AcOEt 4 : 1) 0.40. ^{1}H-NMR spectrum identical to **13**. M.p. 83.8–84.4°, $[\alpha]_D = +181.5$ ($c = 1$ in $CHCl_3$), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, t_R 10.60 min (+) and (+)-**14** (0.49 g) as colorless needles, R_f (heptane/AcOEt 4 : 1) 0.24. ^{1}H-NMR spectrum identical to **14**. M.p. 91.9–92.4°, $[\alpha]_D = +368.5$ ($c = 1$ in $CHCl_3$), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, t_R 9.79 min (+) were obtained.

*(1*R*,2*R*,5*S*,6*S*)-3-(*tert*-Butoxycarbonyl)-6-(methoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid* ((+)-**15**). To a stirred soln. of (+)-**13** (506 mg, 2 mmol) in a mixture of MeCN (6 ml), CCl_4 (6 ml), and H_2O was added $NaIO_4$ (1.75 g, 8.19 mmol) followed by $RuCl_3$ (9.91 mg, 0.044 mmol) at

ambient temp. After stirring for 4 h, the mixture was diluted with CH_2Cl_2 (15 ml) and H_2O (10 ml). The phases were separated, and the aq. phase was extracted with CH_2Cl_2 (2×20 ml). The combined org. extracts were dried (Na_2SO_4), filtered, and concentrated to give 0.565 g of light-red foam, which was purified by FC (AcOEt/AcOH 95 : 5 to give (+)-**15** (543 mg, 90%) as white solid. An anal. sample was recrystallized (AcOEt), ^{1}H-NMR spectrum identical to **15**. M.p. 117.2–118.5°. $[\alpha]_D = +85.6$ ($c = 1$ in $CHCl_3$).

*(1S,2S)-3-[(*R*)-Amino(carboxy)methyl]cyclopropane-1,2-dicarboxylate* ((+)-**17**). A soln. of (+)-**15** (150 mg, 0.50 mmol) in 10% HCl (5 ml) was heated at 100° for 3 h. The soln. was cooled to r.t. and concentrated to deliver 178 mg of crude product, which was submitted to ion exchange chromatography (*Dowex 50WX4*, elution with 12.5% $NH_3 \cdot H_2O$) to give (+)-**17** (98 mg, 82%) as white, hygroscopic foam (diammonium salt), ^{1}H- und ^{13}C-NMR spectra identical to **17**, $[\alpha]_D = +22.3$ ($c = 1$ in H_2O).

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